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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/531,088	03/18/2000	Christopher J. Horvath	10147-22 (MPI2000-131)	5277

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2005 MARKET STREET, SUITE 2200
PHILADELPHIA, PA 19103

EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/531,088	Applicant(s) HORVATH, CHRISTOPHER J.	
	Examin r Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *34-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group I (claims 1-33 and 47-48) in Paper No. 5 is acknowledged.

Claims 34-46 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-33 and 47-48 *are under consideration in the instant application.*

2. Applicant's Petition under 37 CFR 1.10(d), filed 3/31/2000, is acknowledged. However, as set forth in Paper No. 7 (2/6/2002) this Petition has been dismissed.

The filing date of the instant application is therefore considered to be 3/18/2000.

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ***ABANDONMENT*** *of the application.*

4. Applicant's IDSs, filed 1/19/01 and 6/29/01, are acknowledged. Although the Statement in support of the IDS filed 1/19/01 indicates that the cited references were enclosed, they are no longer found as part of the instant file.

The Examiner has re-supplied certain of these references, as indicated by initialing on the attached copy of the 1449. Applicant is invited to re-supply the remaining references for consideration. The Examiner apologizes for any inconvenience to Applicant.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. The disclosure is objected to because of the following informalities: the disclosure lists an $F(abN)_2$ fragment on page 33 at line 28 when it appears that an $F(ab')_2$ fragment is intended. Appropriate correction is required.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Hyperlinks have been noted at least on page 18 at line 24. Applicant is requested to carefully review the specification for additional hyperlinks.

8. Claim 22 is objected to because of the following informalities: the claim recites an $F(abN)_2$ fragment when it appears that an $F(ab')_2$ fragment is intended. Appropriate correction is required.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

10. Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The term "substantially only" in claim 2 is a relative term which renders the claim indefinite. The term "substantially only" is not defined by the claim, the specification does not appear to provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

It is suggested that Applicant provide, if possible, a testable basis for identifying an antibody that binds specifically with "substantially only" the CD18 portion.

B) The term "similar to" in claim 3 is an ambiguous term which renders the claim indefinite. The term "similar to" is not defined by the claim, the specification does not appear to provide a standard or assay for ascertaining what constitutes an epitopic specificity that is "similar to" the referenced antibody.

It is suggested that Applicant provide, if possible, a testable basis for identifying an antibody with an epitopic specificity that is "similar to" that of the referenced antibody.

C) Claims 3-4 are indefinite in the recitation of monoclonal antibody "1B4" because its characteristics are not known. The use of "1B4" as the sole means of identifying the claimed antibody renders the claim indefinite because "1B4" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct antibodies/hybridomas.

Applicant should amend the claim to provide a deposit accession number or other means of distinctly claiming the referenced antibody.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the 1B4 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

Although it appears that the instantly recited 1B4 antibody is the same as the 1B4 antibody deposited with the ATCC under Accession No. HB-10164 and taught in U.S. Pat. No. 5,147,637; there is some ambiguity as to whether or not this is the case because the specification indicates on page 45 at lines 21-23 that the 1B4 antibody is available as ATCC Accession No. TIB10164.

If the instantly recited antibody ***is not the same*** *as the deposited* HB-*10164 antibody*, then Applicant may satisfy the enablement requirement by deposit of the hybridoma/cell line producing the instant antibody.

In addition to the conditions under the Budapest Treaty, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, Applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

NOTE THE CURRENT ATCC DEPOSITORY ADDRESS:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

If the original deposit is made after the effective filing date of an application for patent, Applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state that the biological material which is deposited is the biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See 37 CFR 1.804(b) and MPEP 2406.

If the instantly recited 1B4 antibody ***is the same*** *as that produced by the hybridoma available under ATCC Accession No.* HB-*10164*, then Applicant is required to submit a declaration by a person in a position to corroborate the fact which attests that the error occurring in the specification on page 45 at line 23 (and possibly elsewhere) is an obvious error for which there is an obvious correction; and to provide evidence in support.

For examination purposes, the instantly recited 1B4 antibody is considered to be the same as the antibody produced by the hybridoma of ATCC Accession No. HB-10164.

13. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method employing the 1B4 antibody produced by the HB-10164 hybridoma, does not reasonably provide enablement for methods employing an antibody which has an epitopic specificity that is "similar to" that of monoclonal antibody 1B4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As noted supra, the claims are indefinite in the recitation of an epitopic specificity which is "similar to" that of monoclonal antibody 1B4. In addition to linear sequences, epitopes may be conformation dependent and discontinuous. However, Applicant, as noted supra, has not defined or set forth the metes and bounds of said "similar" epitopes. There is ambiguity and lack of clarity as to the metes and bounds of the phrase "similar". Further, antibodies that can inhibit the binding of the claimed antibody species may block said binding or other functional attributes via steric hindrance as well as via binding the same epitope. In addition, the claims recite a "similar" epitope which can imply that the antibodies recognize more than one epitope. This phrase also reads on small amino acid sequences encompassed by linear or conformational epitopes which are incomplete regions of the epitopes bound by the instant antibodies.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. There appears to be insufficient guidance to any or all of the myriad antibodies that can bind to a myriad of "similar" epitopes encompassed by the instant claims. Particular in view of the ambiguity associated with the instant "similar" epitope, it would be highly unpredictable as to how to either make or use such an antibody. Therefore, it would require undue experimentation to determine said epitopes and identify antibodies with a "similar" epitopic specificity without clearly defining the metes and bounds of said "similar" epitopes. Consequently, the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

14. Claims 1-33 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human and certain other species of the CD18 comprising cell surface molecules Mac-1, LFA-1, p150/p95 and CD11d/CD18, and the natural ligands disclosed on page 3 at lines 16-17 and recited in claim 10; does not reasonably provide enablement with respect to "mammalian proteins which comprise CD18" or other "natural ligands" of cell surface antigens comprising CD18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses and the art recognized several proteins which comprise CD18 (e.g. page 3 at lines 12-15 and claim 7), as well as several natural ligands of these cell surface molecules comprising CD18 (e.g. page 3 at lines 16-17 and claim 10). However, it is unpredictable as to whether Mac-1, LFA-1, p150/p95 and CD11d/CD18 comprise all, some, or only a few of the surface molecules comprising CD18 in any given mammalian species. Similarly, it is unpredictable as to whether the natural ligands recited in claim 10 comprise all, some, or only a few of the natural ligands of these surface molecules comprising CD18. The art recognized that CD18, which is an integrin beta chain, could pair with multiple alpha chains to produce multiple distinct cell surface molecules, each of which could interact with one or more distinct natural ligands (e.g., as reviewed in Ruoslahti J. Clin. Invest. 1991; 87:1-5, especially Figure 2). Given the breadth of the instant claims encompassing any mammalian protein which comprises CD18 or any "natural ligand" of said protein; it would require undue experimentation of the skilled artisan to identify either a representative number of mammalian proteins which comprise CD18, or a representative number of "natural ligands" of cell surface molecules comprising CD18.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance as to the identity of the mammalian proteins comprising CD18 and natural ligands thereof; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

15. Claims 1-33 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite "mammalian protein which comprises CD18" (claim 1 and dependant claims); and "natural ligands" of cell surface antigens comprising CD18 (claims 9-14) as part of the invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

However, there does not appear to be an adequate written description in the specification as-filed of the genus of polypeptides comprising "mammalian proteins which comprise CD18". Although the structure of CD18 is known for certain species such as human, the specification does not appear to establish the essential structural features that identify a protein from a representative number of mammalian species as "CD18" . In addition, although the specification identifies four proteins comprising CD18, the specification does not appear to set forth a structural basis for the interaction of CD18 with other components to form "proteins comprising CD18". The genus of "mammalian proteins which comprise CD18" is very large, both in view of the multiple species encompassed by "mammalian" and because CD18 interacts with multiple other components to produce structurally and functionally distinct "proteins which comprise CD18". Thus it does not appear that the few species known in the art, as set forth in the instant specification, serve as a representative number of species of this very large genus. Nor do the four "proteins comprising CD18" set forth in instant claim 7 provide a representative number of species in the absence of some limitation as to their species of origin since at present they encompass proteins from any mammalian source.

Similarly, there does not appear to be an adequate written description in the specification as-filed of the genus of polypeptides comprising "natural ligands" of cell surface antigens comprising CD18. In this case too, although certain species of "natural ligands" were known (as set forth in the specification and recited in claims 10 and 11), there does not appear to have been established a structural basis for binding to one or more of the known cell surface antigens comprising CD18. Multiple structurally distinct proteins make up the genus of cell surface antigens comprising CD18, each of which can interact with one or more structurally distinct "natural ligands", as noted supra. Thus the specification does not appear to have provided an adequate written description of the genus of "natural ligands" of cell surface antigens comprising CD18. It is noted that instant claims 10 and 11, although limited to particular "natural ligands" still provide neither a species limitation nor alleviate the issues discussed supra with respect to "proteins comprising CD18".

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

17. Claims 1-3, 5-20, 24, 26-33 and 47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Waldmann et al. (U.S. Pat. No. 5,997,867, see entire document), as evidenced by Rogers et al. (WO 98/42360, IDS).

Waldmann et al. teach and claim a method for treating a patient suffering from a leukocyte-mediated reperfusion damage by administering a humanized antibody to CD18 (see entire document, especially claims 1-9 and columns 7-8). Reperfusion damage inherently occurs in a number of conditions associated with increasing blood flow to a blood vessel, such as angioplasty and stent placement (as evidence thereof, see Rogers et al., especially review on pages 1-3). Patients suffering from atherosclerotic or arteriosclerotic blood vessels are patient populations in which such interventional therapies are undertaken to increase blood flow (as evidence thereof, see Rogers et al., especially review on pages 1-3). These patient populations are immediately envisioned by the ordinary artisan as populations subject to reperfusion damage.

Waldmann et al. also teach that the humanized anti-CD18 antibody may be provided to the blood vessel (i.e., "intravenously", e.g., column 8 especially lines 63-67) either prior to (e.g., column 9 especially lines 63-67) or after (e.g., column 9, especially lines 41-47) development of the damage. The antibody of Waldmann et al. would inherently have an epitopic specificity which is "similar to" the 1B4 antibody.

The human CD18 target of the antibody of Waldmann et al. is a human protein and therefore is part of a primate protein that comprises each of Mac-1, LFA-1, (p150, p95) and CD11d/CD18, since each of these bimolecular complexes inherently comprise a CD18 portion and are all expressed *in vivo*. Similarly, administration of the anti-CD18 antibody *in vivo* would inherently inhibit binding of the *in vivo* expressed natural ligands of proteins comprising CD18, including ICAM-1, ICAM-2, ICAM-3, C3bi, Factor X, fibrin and fibrinogen. An inherent outcome of inhibiting this interaction is that functions associated with this binding would inherently be blocked. In addition, neutrophils are leukocytes that inherently express cell surface antigens comprising CD18.

Waldmann et al. also teach and claim the treatment of reperfusion damage post thrombolytic therapy (e.g., claim 6). Therefore Waldmann et al. teach a method wherein the vascular endothelium has been traumatically perturbed, which encompasses the various traumas set forth in claim 16. Although all blood vessels would inherently be treated by administration of an anti-CD18 antibody *in vivo*, the ordinary artisan would immediately envisage treatment of coronary and cerebral blood vessels because these are the primary blood vessels for which intervention to increase blood flow is undertaken.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent in a method comprising administering a humanized anti-CD18 antibody *in vivo* for the treatment of leukocyte-mediated reperfusion damage and the ordinary artisan would immediately envision the recited patient populations as those at risk of reperfusion damage.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-3, 5-33 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867).

The claims are drawn to methods of inhibiting or alleviating stenosis in a blood vessel by administering various forms of an antibody to CD18 to various patient populations associated with reperfusion injury.

Rogers et al. teach that administering antibodies to Mac-1, which is a leukocyte cell surface protein that comprises CD18, reduces neointimal thickening after balloon and stent-induced vascular injury in an animal model of restenosis. Roger et al. further teach that antibodies to Mac-1 can be used in humans to lessen restenosis of blood vessels after revascularization, via angioplasty or bypass surgery, of diseased coronary and cerebral arteries, and lessen stenosis and restenosis of surgically –placed bypass grafts (see entire document, e.g., "Abstract").

Rogers et al. review the art-recognized role of MAC-1 in neutrophil accumulation and migration at sites of vascular injury (e.g., pages 8-9). Rogers et al. further teach that antibody administration blocks binding of Mac-1 (CD11b/CD18) to multiple ligands (e.g., page 9 at line 9-24) and that these ligands include ICAM-1, factor X and fibrin and fibrinogen (page 8 at lines 21-27 and pages 23-24); That various proteins comprised of CD18 are expressed on leukocytes, including neutrophils, is also taught (e.g., page 9, especially lines 9-24). Rogers et al. also teach that functions associated with the binding of a natural ligand to a protein comprising CD18 include binding, translocation and infiltration of leukocytes through the vascular endothelium into intimal vascular tissue (see entire document, especially pages 1-9).

Rogers et al. teach that the administered antibodies may be humanized or used as fragments that are well known in the art (see page 10, especially lines 1-6). Administration of antibody to blood vessels prior to, at the time of, or following injury is taught (e.g., pages 19- 20, especially page 20 at lines 1-6)

Rogers et al. do not teach administering antibodies which bind specifically with substantially only the CD18 portion of a protein.

Although Rogers et al. exemplify an anti-Mac-1 antibody that does not bind substantially to the CD18 portion of Mac-1 because of its broad species cross-reactivity (e.g., page 9), Rogers et al. also clearly recognize that other monoclonal antibodies can be substituted for use in these methods (e.g., page 9, especially in view of the fact that the CD18 portion is the common component shared by the integrins Mac-1. LFA-1 p150,95 and CD11d/CD18 taught as targets on page 8 and pages 23-24).

Waldmann et al. have been discussed supra and in brief teach a method for treating a patient suffering from a leukocyte-mediated reperfusion damage by administering a humanized antibody to CD18 (see entire document, especially claims 1-9). Waldmann et al. further teach that the substitution of a humanized antibody for rat or mouse antibody avoids the unwanted anti-mouse/rat immune response that is elicited when a rat or mouse antibody is administered to a human (e.g., see column 1, especially lines 37-49). Waldmann et al. also teach and claim the treatment of reperfusion damage post thrombolytic therapy (e.g., claim 6).

Waldmann et al., like Rogers et al., also teach that the humanized anti-CD18 antibody may be provided to the blood vessel (i.e., "intravenously", e.g., column 8 especially lines 63-67) either prior to (e.g., column 9 especially lines 63-67) or after (e.g., column 9, especially lines 41-47) development of the reperfusion damage.

Because the antibody of Waldmann et al. binds CD18, it would have an epitopic specificity which is similar to the 1B4 antibody.

Given the teachings of the references, it would have been obvious to the ordinary artisan at the time the invention was made to substitute or combine the humanized anti-CD18 antibody taught by Waldmann et al. for the anti-Mac-1 antibody taught by Rogers et al.

The ordinary artisan would have been motivated to make such a substitution with the expectation that a humanized anti-CD18 antibody would function even better than the antibody of Rogers et al. which recognized the Mac-1 antigen comprising CD18 (CD11b/CD18). The ordinary artisan would have been further motivated to make the substitution because the humanized antibody, unlike the antibody of Rogers et al., would not have been expected to elicit an unwanted immune response to the antibody itself when administered to a human. In addition, the ordinary artisan would have been motivated to substitute an anti-CD18 antibody for an antibody recognizing only Mac-1 because blocking the common CD18 component of 4 integrins, all of which were known at the time the invention was made to be involved in leukocyte recruitment, would be expected to be more beneficial than blocking a single CD18-containing integrin.

Given that the humanized anti-CD18 antibody of US 5,997,867 A was also known to be therapeutic in treating patients suffering in general from leukocyte-mediated disease, including leukocyte-mediated reperfusion damage in general and that due to post thrombolytic therapy; the ordinary artisan would have had a reasonable expectation of successfully substituting or combining the anti-CD18 antibody for the anti-Mac-1 antibody. The various forms of antibody administered (fragments, chimeric, human) appear to represent variations that were well known in the art at the time the invention was made. In addition, given the teachings that administration of anti-CD18 antibodies could be used to inhibit restenosis after interventional therapies such as angioplasty, it would also have been obvious to the ordinary artisan at the time the invention was made to utilize the antibody therapy in the related condition wherein the blood vessel has non-traumatically deteriorated, including for atherosclerosis. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867) as applied to claims 1-3, 5-33 and 47-48 above, and further in view of Wright et al. (U.S. Pat. No. 5,147,637, IDS).

The claims are drawn to a method of inhibiting stenosis in a blood vessel comprising administering the 1B4 antibody.

Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867) as applied to claims 1-3, 5-33 and 47-48 has been discussed supra.

Rogers et al. (WO 98/42360, IDS) in view of Waldmann et al. (U.S. Pat. No. 5,997,867) do not teach the 1B4 anti-CD18 antibody.

Wright et al. teach the 1B4 antibody deposited with the ATCC as HB 10164, and that the 1B4 antibody to CD18 can be used to inhibit the binding of leukocytes to endothelium and their influx into tissues (see entire document).

For the reasons set forth supra one of ordinary skill in the art at the time the invention was made would have recognized that any of a number of antibodies could be substituted into the instant method. Given the teachings of the particular 1B4 antibody and that it binds to CD18 and inhibits leukocyte influx into organs, the ordinary artisan would have had a reasonable expectation that the 1B4 antibody could also be substituted into the methods taught by Rogers et al. in view of Waldmann et al. with a reasonable expectation that the 1B4 antibody would function as expected based upon its specificity and known activity. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 19, 2002

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